Brain-derived neurotrophic factor (BDNF) as a potential mechanism of the effects of acute exercise on cognitive performance

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Keywords: Isoforms | Mediators | Memory | Mental health | Physical activity

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Review

Brain-derived neurotrophic factor (BDNF) as a potential mechanism of the effects of acute exercise on cognitive performance

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Abstract

The literature shows that improvements in cognitive performance may be observed following an acute bout of exercise. However, evidence in support of the biological mechanisms of this effect is still limited. Findings from both rodent and human studies suggest brain-derived neurotrophic factor (BDNF) as a potential mechanism of the effect of acute exercise on memory. The molecular properties of BDNF allow this protein to be assessed in the periphery (pBDNF) (i.e., blood serum, blood plasma), making measurements of acute exercise-induced changes in BDNF concentration relatively accessible. Studies exploring the acute exercise–pBDNF–cognitive performance relationship have had mixed findings, but this may be more reflective of methodological differences between studies than it is a statement about the role of BDNF. For example, significant associations have been observed between acute exercise-induced changes in pBDNF concentration and cognitive performance in studies assessing memory, and non-significant associations have been found in studies assessing non-memory cognitive domains. Three suggestions are made for future research aimed at understanding the role of BDNF as a biological mechanism of this relationship: 1) Assessments of cognitive performance may benefit from a focus on various types of memory (e.g., relational, spatial, long-term); 2) More fine-grained measurements of pBDNF will allow for the assessment of concentrations of specific isoforms of the BDNF protein (i.e., immature, mature); 3) Statistical techniques designed to test the mediating role of pBDNF in the acute exercise-cognitive performance relationship should be utilized in order to make causal inferences.

Keywords: Isoforms; Mediators; Memory; Mental health; Physical activity

1. Introduction

Meta-analytic reviews support that acute exercise has beneficial effects on cognitive performance.[1,2] These effects are reasonably robust, but are generally small in magnitude (effect size (ES) = 0.11–0.20). One direction that is important for future research in this area is to further our understanding of the mechanisms underlying these cognitive benefits. The current lack of understanding concerning mechanisms has created a gap in the knowledge base that has hindered the design of efficient exercise programs intended to generate the largest possible cognitive benefits. Bridging this gap will bring about a vertical growth in knowledge that will ultimately facilitate the creation of exercise prescription strategies that are aimed at improving cognition and brain health.

In reviewing the extant literature, it is clear that there are several active lines of research designed to advance our understanding of how acute exercise may affect cognitive performance. However, much of this work has been focused on the effects of acute exercise on cognitive tasks performed during exercise. For example, Dietrich and Audiffren[3] explained how the reticular-activating hypofrontality model uses a combination of neuroscience, cognitive psychology, and functional neuroanatomy to explain the effects of acute exercise on concomitant cognitive performance and brain activation. Additionally, the relationship between catecholamines (i.e., epinephrine, norepinephrine, dopamine) and cognitive

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performance during acute exercise have been explored.[4] However, the interest of this review is on post-exercise cognitive effects and in particular on the potential role of brain-derived neurotrophic factor (BDNF) as a biological mechanism of the effects. The focus on BDNF is reflective of its demonstrated importance to cognitive performance (i.e., memory),[5,6] its unique molecular properties which allow it to be assessed in the periphery,[7,8] and evidence supporting its responsiveness to exercise.[9]

1.1. BDNF and cognitive performance

As a family of proteins, neurotrophic factors, or "growth factors", are directly involved in neuronal and synaptic growth. The BDNF protein in particular is vital for cognitive performance in the short-term and for adaptations in brain morphology (e.g., plasticity) in the long-term. Indeed, the importance of BDNF for cognitive performance is a line of research that has been given a great amount of attention.[5,6,10] Much of the focus in terms of the effects of BDNF on cognitive performance has been on memory tasks. Since the hippocampus has been identified as a major area of BDNF expression[11] and is widely accepted as being vital to the performance of memory, this is a theoretically appropriate method of cognitive assessment relative to BDNF expression.

The strongest evidence for the role of BDNF in cognitive performance comes from the relatively large body of literature using rodent models to elucidate the role of BDNF on memory. As examples of this strong evidence, there are two particular studies that provide clear demonstrations of the critical role of BDNF in memory. Mu et al.[6] administered neural injections of a BDNF antibody, which effectively deprived the subjects of endogenously expressed hippocampal BDNF, to assess the impact on spatial learning and memory as assessed by the Morris water maze. Their results showed that the animals deprived of BDNF experienced declines in cognitive performance compared to controls, thus illustrating the importance of BDNF for cognitive performance. Conversely, Cirulli et al.[5] took the approach of artificially increasing BDNF to examine the effects on spatial learning and memory. In their study, which was also conducted with rodents and which used a similar form of the Morris water maze, they administered neural injections of exogenous BDNF. Results showed improvements in cognitive performance in rodents that received neural injections of exogenous BDNF compared to controls. Thus, through two different methods of inquiry, these two studies illustrated the importance of the involvement of BDNF in the cognitive processes of spatial learning and memory.

In addition to the animal literature supporting the putative role of BDNF, there is also some very limited evidence with humans. Correlational evidence with older adults has shown that peripheral measures of BDNF (pBDNF) are associated with hippocampal volume and spatial memory.[12] Erickson et al.[12] performed a cross-sectional study, utilizing MRI, enzyme-linked immunosorbent assays (ELISA's), and measures of spatial memory to assess the association between age-related decreases in brain volume, pBDNF, and memory in older adults. Results indicated that older participants had significantly lower concentrations of pBDNF, smaller hippocampal volumes, and worse performance on spatial memory tasks as compared to younger participants. Additionally, the results showed that lower levels of pBDNF were significantly associated with smaller hippocampal volumes and worse memory regardless of the age of the participant. Other studies have demonstrated that there are negative associations between measures of pBDNF and severity of cognitive decline due to Alzheimer's disease.[13,14] Laske et al.[13,14] performed cross-sectional studies to assess pBDNF concentrations between older adults with Alzheimer's disease and healthy controls. Results showed that concentrations of pBDNF were significantly lower in those with Alzheimer's disease compared to controls providing evidence in support of a link between BDNF and cognitive performance. The evidence from these studies illustrates the importance of pBDNF for cognitive performance and brain health, two related but potentially independent constructs, as well as the potential use of pBDNF concentrations as a biomarker for the form and function of the brain.

Research has identified BDNF as playing an instrumental role in the form and function of the brain. In particular, rodent studies have produced robust evidence for the role of BDNF for spatial learning and memory. Additionally, correlational studies in humans have illustrated how BDNF concentrations are not only related to spatial memory performance and the volume of brain regions important for memory in healthy older adults, but are also a potential biomarker for Alzheimer's disease.

1.2. Exercise and BDNF expression

In contrast to the limited evidence supporting a link between pBDNF, brain structure, and brain function in humans, there is a larger body of literature supporting a relationship between acute exercise and pBDNF. This line of research is critical if we are to understand the role of pBDNF as a potential mechanism of the acute exercise-cognitive performance relationship. A recent review by Knaepen et al.[9] described the positive relationship between exercise intensity and pBDNF concentrations. The evidence suggested a dose-response relationship between acute exercise and pBDNF concentrations, with high intensity and graded exercise tests eliciting the greatest exercise-induced increases in pBDNF concentration in healthy participants. Importantly, the increase in pBDNF concentrations following acute exercise has been shown to be somewhat durable following conclusion of the exercise, but to return to baseline levels after a delay of 10–60 min. In addition to the evidence supporting a dose-response effect, there is also evidence that increases in pBDNF concentrations can be observed in response to a variety of exercise protocols and modalities (e.g., step tests, VO_{2max} tests, sub-maximal endurance exercise, sub-maximal sprints).[15–20] Rasmussen et al.[17] and Tang et al.[18] observed effects that highlight the stability of this acute exercise-induced increase in pBDNF in

response to different exercise modalities and protocols. Specifically, Tang et al.[18] utilized a short, 15-min step-exercise protocol while Rasmussen et al.[17] used a longer, 4-h endurance rowing task. While varied protocols hinder the ability to directly compare findings between studies, these results support the robustness of the effect in that the acute exercise—pBDNF relationship is evident in multiple exercise domains.

While many more examples of the acute exercise—induced increase in pBDNF concentrations are provided later in this review (in the context of acute exercise and cognitive performance), it is important to make an initial pronouncement of the existence of these effects. The effect of acute exercise on pBDNF concentrations, along with the previously reviewed effect of BDNF on cognitive performance, are the premise for the potential role of BDNF as a mechanism of the acute exercise—cognitive performance relationship.

2. Measurement considerations in assessing pBDNF in humans

Before continuing to discuss the evidence regarding the role of BDNF in explaining the benefits of acute exercise on cognitive performance, it is important to point out some of the methodological considerations that are relevant to this literature.

2.1. Using peripheral measures of BDNF

First and foremost, conducting empirical studies to explore the role of BDNF in cognitive performance and in the exercise—cognition relationship in humans requires the use of peripheral measures of circulating BDNF (e.g., blood serum or blood plasma). The efficacy of using peripheral measures is supported by research showing the ability of BDNF to pass through the blood—brain barrier[7,8] and positive correlations between concentrations of central (neural) and peripheral measures of BDNF (pBDNF).[17,21] However, it is important to point out that these findings are not equivocal — some authors have argued that BDNF does not cross the blood—brain barrier[22,23] and some studies have not supported a link between pBDNF and central BDNF.[24]

2.2. Source of BDNF measures

In addition to limitations in interpretation that result from our reliance on measures of pBDNF as opposed to central measures of BDNF, it is also important to point out that the particular biological medium from which pBDNF is collected impacts its measurement and interpretation. For example, while pBDNF can be assessed from both blood serum and blood plasma, concentrations have been shown to be as much as 200 times greater in serum compared to plasma.[25] This difference is likely reflective of the methods required to obtain blood serum. In order to obtain measures of pBDNF from serum, samples of whole blood must be allowed to clot prior to collecting aliquots for the performance of ELISAs. Blood platelets have been shown to contain high concentrations of BDNF,[26] and the radical difference between concentrations of BDNF in serum compared to plasma have been suggested to be due to the degradation of platelets during clotting which subsequently releases BDNF into the serum.[25,27] In their review, Knaepen et al.[9] noted these differences in concentrations of pBDNF when assessed in samples from serum compared to plasma and suggested that assessments from plasma reflected concentrations of free-circulating BDNF, while assessments from serum reflected concentrations of BDNF stored in platelets and immune cells. Therefore, it is not appropriate to compare studies assessing pBDNF from differing biological mediums due to the contrasts in inferences that can be made. Greater concentrations of BDNF in plasma may be inferred to be due to increases of free-circulating BDNF and greater concentrations of BDNF in serum may be inferred to be due to increased protein expression and storage. This illustrates the importance for researchers to determine, *a priori*, their theoretical justifications for selecting to assess pBDNF in serum or plasma.

2.3. Variety in methods of assessment

Other methodological issues that hinder comparisons of results between studies include differences in the methods used to assess pBDNF and a general failure to adequately report methodological procedures used in the analysis of pBDNF. As an example, researchers have not been consistent in terms of whether or not statistical adjustments of pBDNF concentrations are made for acute exercise-induced changes in plasma volume. Plasma and serum are both components of whole blood, with serum representing that specific component which is derived from the separation of clotting factors and immune cells. Therefore, changes in plasma volume result in changes in serum volume, and this may result in differences in pBDNF concentration resulting from changes in blood volume and not an increase in expression. This is important because some evidence suggests that significant acute exercise-induced increases in serum pBDNF concentrations may become non-significant after adjusting for changes in plasma volume.[28] For example, Winter et al.[20] reported making a blood volume-based adjustment to serum pBDNF concentration data. However, unlike Brunelli et al.,[28] Winter et al.[20] did not provide a summary of non-adjusted results hence it is not possible to determine the effect of this adjustment on the results obtained from the statistical analyses.

2.4. Isoforms of BDNF

A final consideration relative to this literature is that measures of total pBDNF may not be the critical variable in understanding the extent to which BDNF explains acute exercise benefits on cognitive performance. The central dogma of molecular biology outlines the creation of protein as beginning with DNA that is transcribed into mRNA that is subsequently translated into protein. The resulting protein is affected by posttranslational modifications, such as the cleavage of the polypeptide chain by enzymes. Initially, BDNF, like all

neurotrophins, is translated from mRNA as an immature (pro) isoform and goes through enzymatic cleavage to become a mature (m) isoform. This transformation from proBDNF to mBDNF modifies the signaling pathway of the protein in that each isoform functions in an opposing manner. Alluding to the symbolic representation of philosophies, such as those embodied by Tai Ji Quan and other eastern martial arts, a review by Lu et al.[29] described the "Yin and Yang" approach to understanding the function of the two isoforms. Both isoforms are vital to neural health and performance, yet their interaction with different receptors and signaling pathways result in opposing functions. The stark contrast of these dichotomous functions is illustrated by proBDNF eliciting cell death (apoptosis) and dendritic and synaptic retraction, and mBDNF eliciting cell growth (neurogenesis) and dendritic and synaptic spine formation. This takes place through different signaling pathways, with proBDNF binding to $p75^{NTR}$ receptors and mBDNF binding to TrkB receptors.

The effect of BDNF isoforms on structural changes in the brain are not of concern for acute exercise investigations because these are more long-term effects (which might be of relevance to chronic exercise investigations). However, BDNF isoforms have also been observed to affect neural activity through their association with cellular models of memory (i.e., long-term potentiation and long-term depression).[30,31] In particular, proBDNF has been shown to be important for eliciting long-term depression, while mBDNF is important for eliciting long-term potentiation. This is particularly relevant to those studies exploring the relationship between acute exercise, BDNF, and memory, and provides theoretical justification to explore BDNF as a potential mechanism for this relationship. Additionally, since long-term potentiation has been shown to elicit growth in dendritic and synaptic spines and long-term depression has been shown to elicit dendritic and synaptic retraction, this may explain how BDNF is implicated in the benefits of both acute exercise and repeated bouts of acute exercise (chronic exercise) on cognitive performance. Specifically, because BDNF isoforms play a role in the acute activity of a cell (i.e., long-term potentiation and long-term depression) and because this acute activity influences structural changes in neural morphology, examination of BDNF isoforms may be critical to advancing our understanding of how BDNF mediates the effects of exercise on cognitive performance.

Thus far, researchers have focused exclusively on concentrations of BDNF lacking more fine-grained analyses that focus on BDNF isoforms. Assessments of pBDNF isoform proportions in human blood requires the use of Western blot analyses[32,33] or specifically designed enzyme-linked immunosorbent assays (ELISAs).[34,35] Studies exploring the acute exercise-BDNF relationship have typically used ELISA kits that assess pBDNF concentrations without differentiating between isoforms (e.g., those produced by Millipore, Promega), or specify an assessment of mBDNF noting its slight cross-reactivity with proBDNF (i.e., those produced by R&D Systems). To our knowledge, no acute exercise study has used ELISA kits that assess pBDNF concentrations of specific isoforms (i.e., those produced by Aviscera). However, one study[28] has utilized Western blot analyses to explore effects of acute maximal and submaximal exercise on pBNDF isoform proportions in peripheral blood mononuclear cells. For this study, blood samples were taken prior to (pre), upon completion of (post), and 30 (post-30) and 60 (post-60) min following the acute exercise conditions. Results indicated that both mBDNF and proBDNF levels increased following maximal (i.e., mBDNF: post; proBDNF: post-30 and post-60) and submaximal (i.e., mBDNF: post-30 and post-60; proBDNF: post-60) exercise intensities. Additionally, mBDNF levels were observed to decrease below baseline levels at post-60 following maximal exercise. In stark contrast to these time-dependent and intensity dependent changes in isoforms, non-significant changes in serum pBDNF concentrations, as assessed by ELISA (Promega, Milan, Italy), were observed following maximal exercise. These results suggest that while acute exercise did not increase production of pBDNF (i.e., concentrations), it had a significant intensity-dependent effect on posttranslational modifications (i.e., isoform proportions).

2.5. Summary

Given the theoretical relevance of BDNF to the acute exercise–cognitive performance relationship and the burgeoning evidence supporting that acute exercise impacts BDNF and that BDNF is important for cognitive performance, it is important that future researchers are aware of and work to address these methodological concerns relative to the assessment of BDNF. In reviewing the current literature on acute exercise, BDNF, and cognition, these measurement concerns are apparent and must be taken into consideration as we consider the current state of the knowledge.

3. Acute exercise, BNDF, and cognition

To date, there are only seven studies that have explored the role of pBDNF in the acute exercise–cognition relationship[15,16,20,36–39] (Table 1). These studies use similar paradigms with the typical protocol being that participants perform an acute bout of exercise, pBDNF is assessed prior to and following the exercise, and cognitive performance is assessed prior to and following the exercise. The justification for assessing this relationship is based on the potential role of pBDNF in the acute exercise–cognition relationship.

Ferris et al.[15] used a within-subjects design to explore the potential intensity-dependent nature of the acute exercise-induced change in serum pBDNF concentrations and the resultant effects on cognition. Cognition was assessed with the Stroop Task, a widely used neuropsychological test to assess lower (e.g., processing speed) and higher (executive function) order cognitive processes. Participants performed three intensities of exercise on a cycle ergometer on 3 separate days. Day 1 consisted of a graded maximal test of aerobic capacity (VO_{2max}) while days 2 and 3 consisted of a 30-min bout of low intensity (20% below ventilatory threshold (VT − 20%)) or

Table 1
Details and findings for studies exploring the role of pBDNF as a mechanism of the effects of acute exercise on cognitive performance.

	Participants			Design	Experimental conditions	Modality	Cognitive tasks	Cognitive domain	Source of BDNF	Findings		
	n	Mean age (year)	Sex							Cognitive performance	pBDNF concentration	Effect of pBDNF on cognitive performance
Ferris et al. (2007)[15]	15	25.4	Female and male	Within	a) 20 min: VT − 20% b) 20 min: VT + 10% c) GXT	Cycling	Stroop Task	Executive function	Serum	Improvement in VT + 10% and GXT conditions	Increased in VT + 10% and GXT conditions	Non-significant
Griffin et al. (2011)[16]	47	22	Male	Between	a) 30 min: rest b) GXT	Cycling	a) Face-name task b) Stroop Task	a) Relational memory b) Executive function	Serum	Improvement in memory greatest for exercise group	Increased in exercise group	Not assessed
Winter et al. (2007)[20]	27	22.2	Male	Within	a) 15 min: rest b) 40 min: mod. c) 6 min: high	Running	Language-learning task	Relational memory	Serum	Improved learning and memory in high intensity condition	"Stronger changes" in high intensity condition	Positive association with learning
Lee et al. (2014)[36]	12	24	Male	Within	a) 75 min: 70% VO_{2peak} (W/cooling) b) 75 min: 70% VO_{2peak} (W/out cooling)	Running	a) Digit span b) Symbol-digit c) CRT d) Vigilance task	a) Memory b) Working memory c) Reaction time d) Visual search	Serum	Improved working memory and reaction time in both conditions; Improved visual search in cooling condition; Improved memory in non-cooling condition	Increased in both conditions	Positive association with memory in the non-cooling condition
Skriver et al. (2014)[37]	32	24	Male	Between	a) 20 min: high b) 20 min: rest	Cycling	Visuomotor tracking task	Motor memory	Plasma	Improvement in exercise group	Non-significant	Positive association with memory
Tonoli et al. (2014)[38]	20	30.8	Female and male	Between	a) 22 min: high (diabetic) b) 22 min: high (non-diabetic)	Cycling	a) Stroop Task b) Spatial memory task	a) Executive function b) Relational memory	Serum	Improved executive function in both groups; Improved spatial memory in diabetic group	Increased in both groups	Not assessed
Tsai et al. (2014)[39]	60	22.5	Male	Between	a) Control b) 30 min: mod. (high fitness) c) 30 min: mod. (low fitness)	Running	Visuospatial attention task	Reaction time, P3, CNV	Serum	Improved reaction time in exercise condition; Increased P3 and CNV amplitudes in exercise condition (high fitness group only)	Increased in exercise group	Non-significant

Abbreviations: VT = ventilatory threshold; GXT = Graded Exercise Test (VO_{2max}); Rest = non-exercise control; Mod. = moderate intensity; High = high intensity; CNV = contingent negative variation; CRT = Choice reaction time; pBDNF = peripheral brain-derived neurotrophic factor; W/ = with; W/out = without.

high intensity (10% above VT (VT + 10%)) exercise presented in a randomized order. Results showed increases in pBDNF concentration and improvements in processing speed (i.e., Stroop Task: Word and Color sections) following each exercise condition. However, an improvement in executive function (i.e., Stoop Task: Word-Color section) was only observed in the high intensity condition. Additionally, increases in pBDNF concentrations were not correlated with cognition. These results suggest that while lower-order domains of cognition benefit from the performance of exercise regardless of intensity level, high intensity exercise is necessary to generate benefits in executive function. Based upon their results, Ferris et al.[15] concluded that acute exercise-induced increases in serum pBDNF concentrations are intensity dependent.

Winter et al.[20] also explored the intensity-dependent nature of the acute exercise–pBDNF–cognitive performance relationship. During session one, participants performed a fitness-based physical exercise test in order to obtain information relative to heart rate and lactate concentration. This information was used in the determination of intensity levels for the subsequent exercise conditions. The order of the three experimental conditions was randomized and consisted of a 15-min non-exercise condition (control), a 40-min bout of moderate intensity running, and a high intensity condition requiring the participants to perform two 3-min bouts of sprinting at increasing speeds. Cognitive performance was assessed upon completion of the three experimental conditions by performance on a novel language-learning task immediately after the treatment condition (i.e., learning) and 1-week following completion of the experimental condition (i.e., long-term memory). Concentrations of pBDNF were assessed prior to and upon completion of the experimental condition as well as upon completion of the learning task. Results showed that high intensity exercise benefited learning speed and long-term memory compared to moderate intensity exercise and control. Since information pertaining to total work was not provided, inferences based on between-condition differences in exercise volume cannot be determined and it is important to recognize that the two exercise conditions differed in both intensity and duration. However, the findings suggest that a shorter bout of high intensity exercise is more beneficial to learning and long-term memory than a longer bout of moderate intensity exercise. Due to significant between-condition differences in baseline concentrations of serum pBDNF, the authors interpreted only significant time by condition interactions in pBDNF and did not include results pertaining to potential main effects of time. Results indicated a transient increase in pBDNF and *post hoc* analyses revealed "stronger changes" in pBDNF concentration across time in the high intensity condition compared to the control condition. Additionally, maintenance of pBDNF concentrations post-exercise (i.e., concentrations assessed upon completion of cognitive assessment minus concentrations assessed following exercise) following high intensity exercise were positively correlated with learning performance. Winter et al.[20] concluded that their findings suggest short bursts of high intensity exercise could potentially be used to benefit learning in academic settings (e.g., prior to studying). Additionally, the authors suggest that their findings of an association between maintenance of post-exercise pBDNF concentrations and learning indicate the role of BDNF as a possible mechanisms of the exercise-cognitive performance relationship.

Griffin et al.[16] performed a study to explore how chronic exercise training affects the acute exercise–pBDNF–cognition relationship. However, because of the focus of this review being on acute exercise, only the pre-training acute effects will be discussed. Participants were randomly assigned to either an exercise or sedentary (control) condition. Those in the exercise condition performed a graded maximal exercise test (VO_{2max}) on a cycle ergometer and those in the control group performed a 30-min non-exercise rest period. Assessments of cognitive performance and serum pBDNF were performed prior to and upon completion of the experimental condition and consisted of measures of relational memory (i.e., face-name matching task) and executive function (i.e., Stroop Task). While results showed no effect of exercise on measures of executive function, improvements in memory performance were observed in both groups. The significantly greatest improvement in memory was experienced by those in the exercise group. A transient increase in pBDNF concentration was observed immediately following the exercise, with concentrations returning to baseline levels by 30 min post exercise. It is important to note that pBDNF concentrations were not obtained for the control group. Griffin et al.[16] concluded that improvements in cognitive performance following acute exercise accompanied by increases in pBDNF concentration is suggestive of the potentially "functional role" of pBDNF in the acute exercise–cognitive performance relationship.

Lee et al.[36] used a within-subjects design to explore the relationship between exercise-related hyperthermia and cognitive performance, as well as the relation between exercise-induced changes in pBDNF concentration and cognitive performance. As the effect of hyperthermia on cognitive performance was the main impetus for this study, a non-exercise condition was not used. Participants performed approximately 75 min of running on a treadmill at a speed that correlated with 70% VO_{2peak} in both conditions, and the use of a "neck cooling collar" was counter-balanced. Cognitive performance was assessed at pre- and post-test and consisted of measures of short-term memory (digit span), working memory (symbol-digit modality), reaction time (psychomotor vigilance task), choice reaction time, and visual search (search and memory). Concentrations of serum pBDNF were assessed prior to the performance of cognitive tasks at pre- and post-test. Results indicated that while there were no objective differences in exercise intensity or duration between conditions, significant differences in perceived exercise intensity were observed with participants reporting lower ratings of perceived exertion during the neck cooling collar condition. Significant improvements in measures of working memory (symbol-digit modality) and reaction time were observed in both conditions, while significant improvements in measures of visual search were only observed in the neck cooling collar condition and

significant improvements in short-term memory (digit span) were observed in the no collar condition. Concentrations of pBDNF significantly increased from pre- to post-test in both conditions. Additionally, changes in pBDNF concentration were significantly associated with changes in short-term memory and the magnitude of the association was strong ($r^2 = 0.81$). The authors suggest that when this relationship is considered in the context of the literature base, it is suggestive of BDNF as a biological mechanism that benefits higher order cognitive performance. Measures of perceived heat stress were significantly greater in the no collar condition, and this was interpreted as an increased cognitive load placing an increased attentional demand on participants in this condition. Interestingly, the authors hypothesized that the observation of higher levels of perceived heat stress combined with an association between short-term memory and pBDNF concentration in the no collar condition is indicative of BDNF as a potential selective heat stress-dependent mechanism of the acute exercise-cognitive performance relationship. Future research will be required to explore this novel line of research.

Tsai et al.[39] used a between-subjects design to assess the effect of an acute 30-min bout of moderate intensity treadmill running on cognitive performance (i.e., reaction time on a visuospatial attention task) and underlying neuroelectric signals (i.e., P3 amplitude, contingent negative variation) as well as the relation between exercise-induced changes in serum pBDNF concentration and cognitive performance. The neuroelectric signals are interpreted as providing an indication of readiness to respond to stimuli (i.e., contingent negative variation) or increased attention (i.e., P3 amplitude). Participants were categorized as having high fitness or low fitness, based on results from an initial VO_{2max} test, and were assigned to an exercise condition, consisting of a 30-min bout of moderate intensity exercise performed on a treadmill, or a no exercise (control) condition. Measures of pBDNF were assessed prior to measures of cognitive performance, which were assessed before and after completion of the experimental conditions. Results showed that reaction time improved from pre- to post-test for those in the exercise condition. Results for neuroelectric function indicated that participants in the exercise condition experienced a significant pre- to post-test increase in contingent negative variation amplitude, with only high fitness participants experiencing this increase in electrodes assessing frontal lobe activity (i.e., Fz). Additionally, participants with high fitness experienced significant pre- to post-test increases in P3 amplitude and greater post-test measures of P3 amplitude compared to participants with low fitness and those in the control group. Concentrations of pBNDF increased from pre- to post-test for those in the exercise condition. No correlations were found between the concentration of pBDNF at the pre-test, the concentration of pBDNF at the post-test, or the change in pBDNF from pre- to post-test and measures of behavioral or neuroelectric cognitive performance. The authors concluded that differences in measures of cognitive performance and cognitive function as a factor of aerobic fitness, with better performance and function in higher fit participants, supports the hypothesis of cardiovascular fitness acting as a mechanism of the exercise-cognition relationship. Additionally, the authors propose that these findings also suggest that additional mechanisms may be fitness-dependent.

Tonoli et al.[38] conducted a study to test the effects of acute high-intensity exercise on cognitive performance and BDNF relative to Type 1 Diabetes. A sample of physically active participants with Type 1 Diabetes, were matched (i.e., age, sex, BMI, physical activity) with participants with non-Type 1 Diabetes, and both groups performed a 22-min bout of high intensity exercise on a cycle ergometer. The protocol consisted of a cycling warm-up of 2 min at 100 W, followed by pedaling at 80–100 rpm for 1 min at 90% of the participant's maximal wattage (i.e., determined from a VO_{2max} test performed at a previous session), and ending with a 1-min cool-down at 50 W. With the exception of the warm-up, this protocol was repeated a total of 11 times. Measures of serum pBDNF concentration were assessed prior to assessments of cognitive performance (i.e., Stroop Task, spatial memory) before (pre), upon completion of (post), and 30 min after (post-30) completing the acute bout of high intensity exercise. This study did not utilize a non-exercise control group. Initially, paired samples *t* tests were used to assess baseline and post-test differences in cognitive performance. Results for the Stroop Task indicated that at baseline, participants with Type 1 Diabetes performed significantly worse (reaction time) than matched controls, but both groups experienced significant benefits following exercise (reduced reaction times). Results for the spatial memory task showed that those with Type 1 Diabetes experienced improvements in performance (reduced reaction time) following exercise. Following *t* test analyses, an analysis of covariance (ANCOVA) was used to include pre-test cognitive performance scores as a covariate while assessing post-test differences between groups. Results from this analysis indicated that there were no significant post-test differences in cognitive performance between those with Type 1 Diabetes and those without Type 1 Diabetes. Additionally, baseline concentrations of pBDNF were significantly higher in participants with Type 1 Diabetes compared to matched controls. However, for both groups, pBDNF concentrations increased following high intensity exercise and returned to baseline levels by post-30. No statistical analyses were performed to assess a relationship between pBDNF and cognitive performance. Tonoli et al.[38] concluded that, due to the fact that measures of pBDNF were consistently higher for those with Type 1 Diabetes, pBDNF concentration is affected by Type 1 Diabetes. However, this was not observed to negatively affect the beneficial effects of acute exercise on cognitive performance. The authors suggest further research be performed with non-exercise control groups, which would be needed in order to infer causal effects from exercise, in order to explore the potential metabotropic role of BDNF in the etiology of Type 1 Diabetes.

Lastly, Skriver et al.[37] performed a randomized control trial to explore the relationship between acute exercise, pBDNF concentrations, and motor learning. Motor learning was assessed by performance on a computerized visuomotor

tracking task that required participants to move a curser to trace the curve of a sine wave. The visuomotor tracking task was performed prior to (pre), upon completion of (post), 5 min after (post-5), 10 min after (post-10), 15 min after (post-15), 1 h after (post-1 h), 24 h after (post-24 h), and 7 days after (post-7 days) completing either a 20-min bout of high intensity cycling or a 20-min rest condition (control). Concentrations of plasma pBDNF were assessed at the pre, post, post-5, post-10, and post-15 time points. The high intensity exercise protocol was designed to obtain high levels of blood lactate ($\geq$10 mmol/L) with a short total duration of exercise. The workload was individualized to each participant based on maximal wattages determined during a previous session. Participants performed a 2-min warm-up at 75 W, followed by three bouts of high intensity cycling, separated by two bouts of low intensity cycling. Results indicated that high intensity exercise significantly improved performance of the visuomotor tracking task 24 h after completing the baseline performance. Additionally, while pBDNF concentrations did not increase significantly following high intensity exercise, higher concentrations assessed immediately following exercise (post) significantly correlated with performance on the visuomotor tracking task at post-1 h and post-7 days. Overall, the authors concluded that these observations support the extension of beneficial exercise-induced effects on memory beyond measures of declarative memory. Furthermore, the authors caution that, while results showed associations between motor skill retention and biomarkers associated with the exercise-declarative memory relationship (e.g., BDNF), the correlational analyses inhibit inferences of causality.

In summary, results of this recent literature exploring the effects of acute exercise on pBDNF and cognitive performance and the relationship between the two tend to support that an acute bout of exercise increases pBDNF concentrations when assessed in the blood using either plasma or serum (with Skriver et al.[37] being the only exception). This finding is to be expected given the conclusions drawn in previous reviews that acute exercise increases pBDNF.[9] Results also tend to support that acute exercise benefits cognitive performance, and this is also an expected finding given conclusions from meta-analytic reviews.[1,2] However, there is much less consistency with respect to the evidence regarding the role of BDNF in these cognitive benefits. This lack of consistency may be a result of differences in methodology between studies. In particular, a variety of cognitive measures have been used and the exercise protocols have been implemented in many different ways. With regards to the exercise, many of the studies included high intensity exercise as at least one of their exercise conditions[15,16,20,37,38] however the durations of these protocols varied widely (e.g., two 3-min sprints in Winter et al.[20] compared to eleven 1-min sprints in Tonoli et al.[38]). With respect to the measures of cognitive performance, many of the studies included measures of memory[16,20,36,38] but even then there was great variety in the types of memory assessed (working memory, relational memory, language learning and long-term retention, spatial memory). Other studies measured reaction time, performance on the Stroop Test (inhibition, which is an executive function), visual search (information processing), and a motor tracking task.

Another source of variability in comparing these studies is with regards to how the role of pBDNF was assessed in terms of predicting cognitive performance. This becomes extremely relevant when we attempt to understand what these studies show regarding the relationship between changes in pBDNF and changes in cognitive performance. Although Griffin et al.[16] and Tonoli et al.[38] did not assess relationships between changes in BDNF and changes in cognitive performance, Ferris et al.,[15] Lee et al.,[36] Skriver et al.,[37] Tsai et al.,[39] and Winter et al.[20] did explicitly test for correlations between cognition and exercise-induced changes in pBDNF. Importantly, in studies in which a measure of memory was used,[20,36,37] significant correlations were reported. By contrast, in studies in which memory was not assessed,[39,15] the correlations were not significant. The lack of consistency in findings may be reflective of the focus on different aspects of cognitive performance. Given that memory tasks tend to rely on hippocampal activity while executive functions are frontal lobe-dependent and that the hippocampus is a major area of BDNF expression, it may be that BDNF is only critical to the performance of memory tasks and is not implicated more broadly in explaining the effects of acute exercise on other types of cognitive performance.

4. Overall summary and future directions

The vital role of BDNF for the performance of cognitive tasks is well supported. Observations from rodent studies have shown both benefits and deficits in learning elicited from adding or blocking BDNF, respectively, from the neural environment. Additionally, a single session of exercise has been shown to increase concentrations of pBDNF in an intensity-dependent and transient nature. Studies specifically designed to explore the exercise—BDNF—cognitive performance relationship are limited, but demonstrate increasing interest in this topic. Seven recent studies have assessed the effect of exercise on pBDNF concentration and cognitive performance, and results from three of these support that increases in pBDNF are associated with improvements in memory.

In thinking of how to advance this important line of research, it is critical to consider theoretical underpinnings and methodological issues. For example, with regards to identifying cognitive measures for future studies, it is important for selections to be made based upon relevance to theoretical underpinnings. The theoretical foundations of explorations into the acute exercise—pBDNF—cognitive performance relationship are derived from literature concerning rodents and chronic exercise. The chronic exercise rodent literature provides the strongest evidence of the mediating role of BDNF in the exercise—BDNF—cognitive performance relationship,[40] and both rodent and human literature has shown positive effects of chronic exercise on hippocampal volume.[41,42] Additionally, chronic exercise has been shown to increase BDNF mRNA and protein concentrations in the hippocampus,[11,43] while acute exercise had been shown to increase BDNF concentration in the periphery. These results comprise a

theoretical justification to use cognitive assessment tools that measure hippocampus-dependent cognitive domains (e.g., relational memory). Perhaps serendipitously, this type of memory assessment has been used in many rodent studies in the form of spatial learning and memory tasks (e.g., Morris water maze, Radial arm maze). However, by contrast, studies with humans have included measures of memory, executive function, and other various cognitive measures. Although BDNF may play a role in explaining the effects of acute exercise on the spectrum of cognitive measures, based upon theory and empirical evidence from non-human animal studies, it is suggested that the exploration of the acute exercise–pBDNF–cognitive performance relationship might benefit from a focus on hippocampal-dependent processes.

Another important direction for future research is to use more fine-grained measures of BDNF to allow for an examination of BDNF isoforms. Particularly, in order to take the divergent signaling pathways of pBDNF into consideration, the investigation of specific BDNF isoform proportions in the exercise–cognition relationship should be considered. Given that Brunelli et al.[28] observed changes in pBDNF isoform proportion in response to acute physical activity and that the BDNF isoforms have distinct and opposing functions, this is an important direction for future research.

Lastly, future studies should use experimental designs and statistical techniques that allow for inferences of causation. In the current literature, researchers have used correlational analyses to test relationships between changes in pBDNF and changes in cognitive performance. However, these correlational analyses do not allow for inferences of causation and, hence, do not appropriately assess the extent to which BDNF actually mediates the effects of acute exercise on cognitive performance. With regards to experimental design, Maric et al.[44] suggest 10 different ways of strengthening mediation analyses, including the inclusion of appropriate non-exercise control groups. With regards to statistical analyses, future research should take advantage of recent advances in mediation analyses, the appropriate statistical techniques (i.e., testing of indirect effects by bootstrapping)[45] that make causal inferences possible.

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